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Citizen Petition

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Fish & Richardson P.C. submits this petition on behalf of Allergan, Inc. requesting FDA to refuse or suspend approval of any Abbreviated New Drug Application ("ANDA") for brimonidine tartrate ophthalmic solution ("BTOS"), 0.2%.[1] This petition is submitted under 21 C.F.R. § 314.127(a)(11) and 314.161(a)(1), and Section 11 of the Best Pharmaceuticals for Children Act, PL 107-109, 115 Stat. 1408 ("BPCA").

I. STATEMENT OF GROUNDS

The FDA should refuse (or suspend) approval of all ANDAs for a 0.2% ophthalmic solution of brimonidine tartrate for two separate reasons.

First, Allergan has voluntarily withdrawn ALPHAGAN® BTOS 0.2% in lieu its the FDA-approved ALPHAGAN P® BTOS 0.15% because ALPHAGAN P® BTOS 0.15% has a better safety profile with a lower incidence of allergy than ALPHAGAN® BTOS 0.2%.[2] Allergan thus, withdrew ALPHAGAN® due to

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[1] Allergan submits this petition in response to a letter from Gary J. Buehler, Director of OGD, dated September 26, 2002. Allergan also submits this petition in response to the August 27, 2002, Citizen Petition filed by Alcon Research, Ltd. and the August 30, 2002, Citizen Petition submitted by Ivax Pharmaceuticals, Inc.

[2] ALPHAGAN P®'s improved safety profile with lower incidence of allergy results in improved efficacy because fewer patience have to disrupt their glaucoma treatment due to allergic reaction.

"safety and efficacy reasons" as contemplated under 21 C.F.R. § 314.161. Accordingly, FDA should refuse approval of any ANDAs for generic BTOS 0.2% as required under 21 C.F.R. § 314.127(a)(11) to ensure that patients are not prescribed a "less safe" formulation of this drug.

Second, because Allergan has pediatric labeling exclusivity for ALPHAGAN® BTOS 0.2% under 21 U.S.C.§355a(c)(1)(A)(ii) until June 20, 2005, but has withdrawn the drug, FDA has no means of ensuring the safety and efficacy of generic BTOS 0.2% in the pediatric population. At minimum, FDA should suspend approval of all ANDAs for BTOS 0.2% until ALPHAGAN®'s pediatric labeling exclusivity expires to prevent adverse and potentially life-threatening reactions to these generic products in the pediatric population.

A. Background

On September 6, 1996, FDA approved Allergan's NDA No. 20-613 for ALPHAGAN® BTOS 0.2% for the treatment of open-angle glaucoma. The FDA then listed this drug in its Approved Drug Products with Therapeutic Equivalence Evaluations, known as the "Orange Book."

1. ALPHAGAN® BTOS 0.2% Pediatric Labeling Exclusivity

In June of 1999, FDA requested Allergan to conduct pediatric studies on ALPHAGAN®. Allergan responded by conducting a multi-site international clinical study on the pediatric population. This study disclosed several important side effects in children, including incidence of somnolence in every stratum from two to seven years of age.[3]

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[3] The incidence of somnolence in children aged 2-6 was 50-83%. The incidence dropped to 25% for children aged 7 years and older.

Based on the study results, on December 20, 2001, FDA awarded Allergan three years and six months of pediatric exclusivity under 21 U.S.C. §355a(c)(1)(A)(ii). ALPHAGAN®'s pediatric labeling exclusivity expires on June 20, 2005. This pediatric labeling discloses the adverse affects discovered in Allergan's pediatric studies. It also recommends that ALPHAGAN® not be used in patients under 2 years of age.

2. Approval of ALPHAGAN P® BTOS 0.15%

On March 16, 2001, FDA approved Allergan's NDA No. 21-262 for ALPHAGAN P® BTOS 0.15%, also for the treatment of open-angle glaucoma. This drug product not only has a lower concentration of brimonidine than the approved 0.2% solution, but also contains a different preservative—Purite® (sodium chlorite)—instead of the benzalkonium chloride used in ALPHAGAN® BTOS 0.2%. Through its clinical trials, Allergan demonstrated that the 0.15% has a much lower incidence of allergy—greater than 40% lower—than the 0.2% solution. This improved safety profile is particularly important for glaucoma patients because incidence of allergy is a leading reason for patient inability to comply with a glaucoma treatment regimen. In other words, a higher incidence of allergy to ophthalmic solutions in glaucoma patients equates to decreased safety and results in overall decreased efficacy because allergic patients are not able to maintain continuous treatment.

3. Withdrawal of ALPHAGAN® BTOS 0.2% from the Market

After a year of marketing, in which clinical practice confirmed that ALPHAGAN P® was safer and resulted in improved patient compliance than

ALPHAGAN® [4]and Allergan determined that it could supply sufficient quantities of ALPHAGAN P® to cover ALPHAGAN® prescriptions, ALPHAGAN® was withdrawn from the market. On August 20, 2002, Allergan notified CDER under 21 C.F.R. § 314.81(b)(3)(iii) that it was withdrawing ALPHAGAN® (but not the NDA) from sale. Currently, there is no BTOS 0.2% product being supplied to the market; rather, the safer BTOS 0.15% is readily available and is being prescribed to glaucoma patients.

4. Submission of Three Different ANDAs for generic BTOS 0.2%

Around October 2001, Alcon Laboratories, Inc. ("Alcon") and Bausch & Lomb ("B&L") each filed ANDAs (Nos. 76-254 and 76-260 respectively) requesting FDA approval to market a generic BTOS 0.2%. Around August 2002, IVAX Pharmaceuticals, Inc. (IVAX) filed a third ANDA (No. 76-372) also requesting FDA approval to market BTOS 0.2%. On August 27, 2002, Alcon Research filed a Citizen Petition, as did IVAX on August 30,2002, requesting FDA to "provide a determination whether the listed drug [ALPHAGAN®] has been voluntarily withdrawn for safety or effectiveness reasons."

B. FDA Should Refuse Approval of ANDAs for BTOS 0.2% Because Allergan Withdrew this Product from the Market for "safety and efficacy reasons" in Lieu of the Safer BTOS 0.15% Formulation

Market withdrawal of a drug is governed by 21 C.F.R. §314.127(a)(11), which states that:

> FDA will refuse to approve an abbreviated application for a new drug under section 505(j) of the act [when] . . . FDA has determined that the

[4] Twelve months is an acceptable minimum period to determine the allergic response of a drug in glaucoma patients.

> reference listed drug has been withdrawn from sale for safety or effectiveness reasons under Sec. 314.161, or the reference listed drug has been voluntarily withdrawn from sale and the agency has not determined whether the withdrawal is for safety or effectiveness reasons . . . .

As noted, Allergan withdrew the listed drug ALPHAGAN® BTOS 0.2% from the market because it results in a greater incidence of allergy than the ALPHAGAN P® BTOS 0.15%. To be clear, Allergan did not withdraw ALPHAGAN® BTOS 0.2% because it is unsafe. Rather, Allergan withdrew the 0.2% solution from sale "for safety and efficacy reasons" as contemplated by 21 C.F.R. § 314.161 because a safer 0.15% formulation, resulting in greater efficacy in the overall patient population, became available in the market. Because Allergan withdrew the listed drug, BTOS 0.2%, from sale for safety and effectiveness reasons, FDA should refuse to approve any ANDAs for BTOS 0.2% as required by 21 C.F.R. § 314.127(a)(11).

C. FDA Should Refuse Approval of ANDAs for BTOS 0.2% Because FDA no Longer has a Means of Ensuring the Safety of This Formulation in the Pediatric Population

As the FDA recently explained, its task in implementing Section 11 of the BPCA "is to ensure that labeling for ANDAs adequately protects pediatric health and is consistent with marketing exclusivity for the innovator."[5] Because Allergan has pediatric labeling exclusivity for its BTOS products until August 20, 2005, but has withdrawn the BTOS 0.2% formulation from the market, FDA cannot ensure that labeling for a generic BTOS 0.2% formulation will adequately protect pediatric health. In other words, no generic can use ALPHAGAN®'S pediatric labeling until

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[5] FDA's Jan 24, 2002 Response to Bristol-Myers Squibb Company's Citizen Petition of December 26, 2001, p. 3.

Allergan's label exclusivity expires, but approval of a generic BTOS 0.2% formulation without the pediatric labeling would be unsafe for children.

Every prescription drug, as is well known, has side effects. Side effects in children often differ greatly from the side effects experienced by adults.[6] The BTOS 0.2% formulation is a case in point. Here, Allergan's pediatric studies showed that BTOS 0.2%, when given to children between 2 and 6 years of age, resulted in 50-83% incidence of somnolence, with a 25% incidence of somnolence in children age 7.

To ensure the safety of listed drugs and their generic counterparts for use in children, FDA requires these products to disclose instructions and warnings for pediatric use on their labels. 21 C.F.R. § 201.57. During the period of pediatric labeling exclusivity, however, generics cannot label the protective pediatric information of the listed drug. Section 11(a) of the BPCA authorizes the FDA to approve generics with omitted pediatric information or to allow generics to use contraindications, warnings, or precautions taken from the protected pediatric label, provided that such omitted information or selective disclosures do not make the generic label false or misleading and do not make the drug unsafe for use in children.

This alternative to full generic pediatric labeling, however, logically requires the listed drug to exist on the market. In the case of BTOS 0.2%, the reference listed drug has been withdrawn from the market and is no longer listed in the Orange Book. Without a complete label for reference, a generic BTOS 0.2% formulation is demonstrably unsafe for use in children regardless of the BPCA's labeling alternative. For example, even if the FDA allowed generic BTOS 0.2% manufacturers to add a

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[6] Rodriguez, William J., CDER's experience: What We Have Learned From the Pediatric Initiative, www.fda.gov.cder/pediatric.

warning of potential coma in children under the age of two to their label (per Section 11 of the BPCA), without the ALPHAGAN® label's detailed discussion of the significant occurrence of somnolence in older children, healthcare professionals run the risk of underestimating the drug's possibility of causing severe central nervous system effects in a young child.[7]

Moreover, serious side effects frequently do not emerge during clinical trials but are identified only after a product has been approved and widely prescribed to the general population.[8] Again, the BTOS 0.2% formulation is a case in point. A report which Allergan submitted to the FDA on August 30, 2002, details the unexpected onset of coma resulting from an accidental ingestion of ALPHAGAN® by a 50-day-old infant.

Physicians have been prescribing BTOS 0.2% to children ever since Allergan first began marketing ALPHAGAN® in 1996. In fact, before FDA requested Allergan to run pediatric clinical trials on ALPHAGAN®, Allergan had already received several spontaneous reports of serious and potentially life-threatening adverse events (e.g., coma) in infants resulting from use of ALPHAGAN®. Pediatric prescription volumes of BTOS 0.2% have been on the rise since FDA granted Allergan its pediatric labeling exclusivity less than one year ago, however, because the pediatric approval and extensive pediatric use are so new, the side effects profile in pediatric patients is not yet well documented. The continued use of a BTOS 0.2%

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[7] See, e.g., Ass'n of Am. Physicians and Surgeons, Inc., v. United States Food and Drug Admin., Civil Action 00-02898, slip op. at *3-4 (D.D.C. October 17, 2002).

[8] Lumpkin, Dr. Murray, Meeting No. 74 of Endocrinologic and Metabolic Drugs Advisory Committee, Center for Drug Evaluation and Research, Food and Drug Administration, May 19, 2000 at 38-54

formulation in the pediatric population may unveil additional and/or increased side effects.

To deal with such matters, FDA typically requires the manufacturer of the listed drug to periodically update its labeling to identify newly discovered side effects and to address foreseeable concerns, such as ingestion. 21 C.F.R. § 314.70(b)(3). Among other things, such labeling updates ensure continued pediatric safety for both the listed drug and its generic counterparts. However, in the present situation, because the listed drug has been withdrawn, pediatric labeling for BTOS 0.2% will not be updated and generic versions of the listed drug will put patients at risk.

In summary, because the BTOS 0.2% listed drug has been withdrawn from sale but Allergan maintains protected pediatric labeling for such drug until August 20, 2005, a generic BTOS 0.2% formulation cannot be adequately labeled and will not be updated to ensure safety in pediatric use. In compliance with the BPCA and FDA's own regulations, and to ensure marketed medications are safe and effective for all populations to whom they are prescribed, FDA should, at minimum, suspend approval of all ANDAs for generic BTOS 0.2% until Allergan's pediatric labeling exclusivity has expired.

II. ENVIRONMENTAL IMPACT STATEMENT

This petition is categorically excluded from the environmental impact statement requirement under 21 C.F.R. § 25.31.

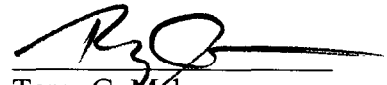
III. ECONOMIC IMPACT STATEMENT

The Commissioner has not requested economic impact information at this time.

IV. CERTIFICATION

The undersigned certifies that, to the best of his knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information know to the petitioner which are unfavorable to the petition.

Respectfully Submitted,



Terry G. Mahn

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